

[received by the International Bureau on 19 Mars 2003 (19.03.03); original claims 1-31 replaced by new claims 1-31 (5 pages)]

1. A compound according to Formula 1

Formula 1

in which Z is selected from the group consisting of an alkyl, an O-alkyl, an alkenyl, an alkynyl, and CN, wherein the alkyl, the alkenyl, or the alkynyl is optionally substituted with a halogen or OH;

A is CH or N, and E is C-R₆ or N, such that (1) when A is CH then E is C-R₆ or N, and (2) when A is N then E is CH;

X is NR₁R₂, NR₂NR₃R₄, NR₂N=NR₃, NR₂N=CHR₃, NR₂N=O, NR₂C(=O)NR₃R₄, NR₂C(=S)NR₃R₄, NR₂C(=NH)NR₃R₄, NR₁C(=O)NR₂NR₃R₄, NR₂OR₃, ONHC(O)O-alkyl, ONHC(O)O-aryl, ONR₃R₄, SNR₁R₂, SONR₁R₂, or S(O)₂NR₁R₂;

wherein R₁, R₂, R₃, and R₄ are independently H, alkyl, substituted alkyl, O-alkyl, cyclic alkyl, heterocyclic alkyl, alkoxy, alkaryl, aryl, heterocyclic aryl, substituted aryl, acyl, substituted acyl, S(O)₂-alkyl, NO, NH₂, or OH; and

R₆ is H, NH₂, halogen, N₃, NHR₁, NHCOR₁, NR₁R₂, NHSO₂R₁, NHCONHR₁,

NHCSNHR₁, CH₂NHR₁, CHR₁NHR₂, NHNH₂, CN, alkyl, alkenyl, alkynyl,

CH₂-aryl, CH₂-heterocycle, halogen, OH, or SH; and

wherein combination of the radicals A, E, X, and Z confer antiviral activity against HCV to the compound.

- 2. The compound of claim 1 wherein A and E are CH, Z is CH₃ and wherein X is NR₁R₂.
- 3. The compound of claim 2 wherein R₁ is CH₃, NH₂, or H, and wherein R₂ is CH₂CH₂OH, CH₂CH₂NH₂, OCH₃, CH₃, or OH.
- 4. The compound of claim 1 wherein A and E are CH, Z is CH₃ and wherein X is NHNR₃R₄.
- 5. The compound of claim 4 wherein R₃ is H, or CH₃, and wherein R₄ is H, CHO, C(O)CH₃, C(O)OCH₃, S(O)₂CH₃, or CH₃.
- 6. The compound of claim 1 wherein A and E are CH, Z is CH₃ and wherein X is ONHC(O)O-alkyl or ONHC(O)O-alkaryl.
- 7. The compound of claim 6 wherein ONHC(O)O-alkyl is ONHC(O)OC(CH₃)₃, and wherein ONHC(O)O-alkaryl is ONHC(O)O-CH₂-phenyl.
- 8. The compound of claim 1 further comprising a moiety covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, thereby replacing the OH group at the at least one of the C2'-atom, C3'-atom, and C5'-atom, and wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ.
- 9. The compound of claim 8 wherein the moiety comprises a cyclic phosphate, a cyclic phosphonate, or a cyclic phosphoamidate.
- The compound of claim 8 wherein the moiety has a structure according to Formula
 M1 or Formula M2

$$\begin{array}{c} O \\ A - P - BR_1 \\ B'R_2 \end{array}$$

wherein A in M1 or M2 is O or CH₂ and replaces the 5'-OH group of the compound of Formula 1;

M1

- B and B' are independently O or NH, and where at least one of B and B' is NH then at least one of R₁ and R₂ is an amino acid that forms a peptide bond with the N atom of the NH, respectively, and where at least one of B and B' is O then at least one of R₁ and R₂ is CH₂CH₂SC(=O)t-butyl or CH₂OC(=O)iPr; and
- V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, chlorophenyl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH2aryl.
- 11. The compound of claim 1 further comprising a phosphate group covalently coupled to the C5'-OH group to form a phosphate ester.
- 12. A dinucleoside compound according to Formula 2

Formula 2

wherein X and X' are independently NH, N-alkyl, or N-substituted alkyl;

- Y is (CH₂)₁₋₁₀, (CH₂CH₂O)₁₋₃, (CH₂CH₂S)₁₋₃, a heterocyclic ring, or an aromatic ring; and
- Z and Z' are independently selected from the group consisting of an alkyl, an O-alkyl, an alkenyl, an alkynyl, and CN, wherein the alkyl, the alkenyl, or the alkynyl is optionally substituted with a halogen or OH.
- 13. The compound of claim 12 wherein Z is CH₃, and wherein X is NH.
- 14. The compound of claim 13 wherein Y is (CH₂)₁₋₁₀.



- 15. The compound of claim 12 further comprising a moiety covalently coupled to at least one of the C2'-atoms, C3'-atoms, and C5'-atoms, thereby replacing the OH group at the at least one of the C2'-atoms, C3'-atoms, and C5'-atoms, and wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ.
- 16. The compound of claim 15 wherein the moiety comprises a cyclic phosphate, a cyclic phosphonate or a cyclic phosphoamidate.
- 17. The compound of claim 15 wherein the moiety has a structure according to Formula M1 or Formula M2

$$\begin{array}{c} O \\ A - P - BR_1 \\ B'R_2 \end{array}$$

$$M1 \qquad \qquad M2$$

wherein A in M1 or M2 is O or CH₂ and replaces at least one of the 5'-OH groups of the compound of Formula 2;

- B and B' are independently O or NH, and where at least one of B and B' is NH then at least one of R₁ and R₂ is an amino acid that forms a peptide bond with the N atom of the NH, respectively, and where at least one of B and B' is O then at least one of R₁ and R₂ is CH₂CH₂SC(=O)t-butyl or CH₂OC(=O)iPr; and
- V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, chlorophenyl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH₂aryl.
- 18. The compound of claim 12 further comprising a phosphate group covalently coupled to at least one of the C5'-OH groups to form a phosphate ester.
- 19. A pharmaceutical composition comprising a compound according to claim 1, claim 10, claim 12, or claim 17, wherein the compound is present at a concentration effective to reduce viral propagation of a virus in a patient infected with the virus.



- 20. The composition of claim 19 wherein the virus is selected from the group consisting of an HCV virus, an HRV virus, an RSV virus, an HIV virus, and an HBV virus.
- 21. The composition of claim 19 further comprising a second pharmacological molecule.
- 22. The composition of claim 21 wherein the second pharmacological molecule comprises an interferon.
- 23. A method of treating a viral infection in a patient comprising administering a compound according to claim 1, claim 10, claim 12, or claim 17 to the patient in an amount effective to reduce viral propagation.
- 24. The method of claim 23 wherein the compound is a compound according to claim 1 and wherein the virus is an HCV virus.
- 25. The method of claim 23 wherein the compound is a compound according to claim 10 and wherein the virus is an HCV virus.
- 26. The method of claim 23 wherein the compound is a compound according to claim 12 and wherein the virus is an HCV virus.
- 27. The method of claim 23 wherein the compound is a compound according to claim 17 and wherein the virus is an HCV virus.
- 28. A method of reducing viral propagation in a cell infected with a virus, comprising presenting the cell with a compound according to claim 1, claim 10, claim 12, or claim 17 to the cell in an amount effective to reduce viral propagation.
- 29. The method of claim 28 wherein the virus is selected from the group consisting of an HCV virus, an HRV virus, an RSV virus, an HIV virus, and an HBV virus.
- 30. The method of claim 29 wherein the compound is converted in the cell to a metabolite that reduces viral propagation.
- 31. The method of claim 30 wherein the metabolite comprises a phosphate group that is covalently coupled to the C5'-atom via an ester bond with the C5'-OH group.